DOI: 10.31703/gdddr.2019(IV-I).04
URL: http://dx.doi.org/10.31703/gdddr.2019(IV-I).04 Vol. IV, No. I (2019) Pages: 34 – 40

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A Comprehensive Insights of the Multiple Dose Regimen

Abstract *A multiple dose regimen is a concept that is used for certain diseases as arthritis, heart diseases etc. It is used to increase the therapeutic activity and clinical efficacy of the drugs. Drugs are usually used in single doses to produce acute effect but in cases where chronic affect is required multiple dosage regimen is required. Designing the dosage regimen and maintaining the drug concentration in blood plasma after administration are the primary goals to achieve safety and efficacy. That is to maintain drug concentration in therapeutic window. Moreover, the IV infusion and continuous IV diffusion is reviewed.*

Key Words: Multiple Dose Regimen, Loading Dose, Drug Accumulation, IV Infusion, Pharmacokinetics

Introduction

With the advancement in science and technology new procedures are being introduced to improve the living standards. Amini, M. Reis, M. Wide-Swensson, D. A. (2020)

Dosing frequency and required dose are determined by the pathway a drug takes when administered. To obtain the optimal effect of the therapy the multiple dosage regimen is used. Multiple dosage regimen can be defined as the administration of the drug substance in appropriate doses and at appropriate time intervals in required dose to maintain the concentration of drug in plasma throughout the entire therapy period drug remains in the therapeutic window. Pharmacokinetic parameters of a drug remains constant during the entire course of the therapy after the proper dosage regimen is established. One compartment model calculation is also applicable to the two compartment models.

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- Drug Administration at fixed dose and fixed interval

There are two major parameters to design a drug dose regimen these are

- Dose size
- Dosing frequency i.e. intervals between two subsequent doses

Multiple dosage is used in case of being chronic disease two-compartments, heart diseases where long courses are required, unlike single dose regimen that is used in case of acute conditions.

Drug administration at fixed interval and dose

Dose:

Appropriate quantity of drug needed to produce required response.

It can be also defined as;

Quantitative dosage that estimates the quantity of the drug substance required to produce a biological response after administration is called dose size.

Fixed Dose

Repeated administration regimen is the most widely used approach to the expenditure of the therapy of drug.

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- Upon the administration of the drug before the previously given dose is completely excreted from the body, results in the accumulation of the drug substance in the body.
- When the amount of the drug or the rate of drug into the body is equal to the rate of the drug out of the body means administration is equal to the elimination the average drug concentration reaches the plateau or steady state.
- At the plateau state, the quantity of the drug substance eliminated in each equal interval becomes equal to the quantity of the drug administered that can be determined by multiplying the dose with the bioavailability. Plasma concentration curve shows similar trend between the doses of drugs for each dosing interval.

Dose at Fixed Interval

Chronic diseases are treated usually by the multiple doses of drugs for example hypertension and arthritis. Upon the administration of the single dose of drug the drug plasma level quickly increases and reaches the MEC and then in the therapeutic window and after some time it falls below the MEC causing the reduction in the effect. Fan J, de Lannoy I., A. (2014 Jan 1) If the drug is continuously administered at the fixed dose in regular intervals then the amount of drug in the body will start to rise until it will reach the steady state which means that constant plasma level and then peak concentration can be obtained by the preliminary dose.

Importance of Multiple Dose Regimen

Drug is accumulated inside the body if the second dose of the drug is administered to the person before the completion of the interval to eliminate the previously administered dose. Following the administration of single dose drug concentration rises and then falls below the minimum effective concentration MEC leading to the reduced therapeutic effect. Therefore, to enhance the therapeutic effect of the drug, it can be administered in multiple doses according to a regimen. Plasma concentration of the drug must remain within the therapeutic index to achieve the clinical outcome of the drug. Multiple drug dosage regimen is developed to provide the long-term delivery of the drug maintaining its concentration within narrow limits.

Criteria for Optimum Dosage Regimen

Optimum dosage regimen criteria depend upon these

- Drug concentration must be within narrow limits in the therapeutic index
- Should be convenient for the patient

Design of the drug dosage regimen is dependent upon these

- The dose size of the drug
- Dosage frequency i.e. time interval in between the doses

Superposition Principle

Superposition principle applies to the linear pharmacokinetic parameters, which means when the ADME is linear.

Hence the drug concentration after each dose can be added to calculate the concentration of drug after multiple doses.

Basic Assumptions for Superposition Principle

These are the two major basic assumptions for superposition principle

- Drug elimination must follow the linear kinetics
- PK of the drug does not change after multiple doses.

Drug Accumulation

Without the elimination of the already given dose, next administration of drug will contribute to the accumulation of drug in body by increasing the residual amount of drug that is already present in the body. Ambrose P. G., et al. (2007)

Smaller the interval of dosage administration as compared to the elimination interval then the amount of the drug that is residual will also be more upon the ingestion of the next dose as a result the drug can remain in body more extensively. Plateau state is ultimately achieved because the drug substance cannot accumulate over an indefinite period of time as a specific frequency of drug administration. The reason for this is that the elimination of a drug is actually dependent upon the concentration of the drug.

Higher the concentration of the drug more the elimination of drug from the body. If the two doses are missed, then the plateau concentration will fall below the therapeutic window as a result again a longer interval is required to regain that desired level of drug concentration in the plasma.

If the dose is divided in the several small doses, then the average plasma concentration of the drug shows small variation.

Time needed to reach the plateau state accumulation in the multiple dosage regimen is dependent upon the elimination rate. Plateau state declines to a recent value resulting in a new elimination rate. If there is no sufficient elimination of the drug, then the average plasma concentration of the drugs eliminated via renal pathway increases and can cause toxicity.

Intravenous Infusion

Intravenous therapy (IV) is a therapy that delivers fluids exactly into a vein. The intravenous route of administration can be used both for *injections*, using a syringe at higher pressures; as well as for *infusions*, typically using only the pressure supplied by gravity. Intravenous infusions are commonly pertained to as *drips*.

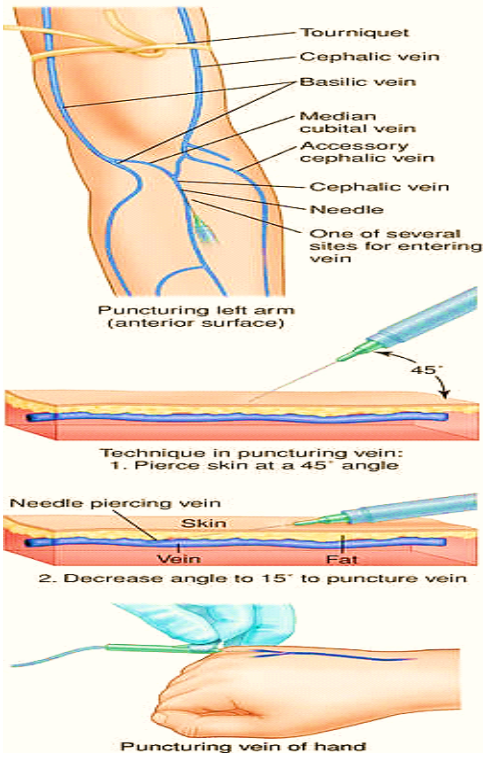


Figure 1: Method to administer an IV Infusion

Purpose of IV infusion

These are some of important purposes of IV infusion

- This strategy of liquid substitution is utilized most frequently
- Used to preserve liquid and electrolyte balance,
- Used to adjust liquid volume shortfalls after intempe rate misfortune of body fluids,
- Used in patients incapable to require adequate volumes orally
- Maintenance of steady plasma concentration
- Dosage adjustment

Advantages of IV Infusion

These are the advantages of IV infusion

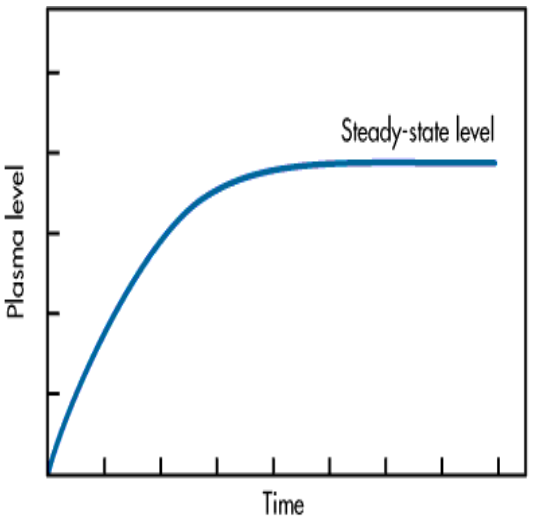
- Easy get to quick organization of solutions
- Continuous or irregular organization of nutrients
- Rapid changes in circulatory system
- Easy to screen conveyance of liquids, electrolytes, and supplements (for those with disabled GI tracts.)

One Compartment Model drugs IV Infusion

The one-compartment open model is the best method to portray the method of drug distribution and elimination within the body. This model assumes that the drug can enter or leave the body (i.e., the model is "open"), and the complete body acts like a single, uniform compartment.

Steady state or plateau Level

The plasma drug concentration–time curve of a drug given by consistent IV mixture is shown in Figure (graph).



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Figure 2: Steady state level

Method

Upon infusing the drug via intravenous route at a constant rate will result in the first order kinetics in a frequent way to be attained. When the infusion is started then the amount of drug in the body is zero because no elimination is there. The addition of the drug concentration inside the body at the point when it is rising is increased but the elimination rate also. Therefore, the rate of elimination will continue to increase until it reaches the infusion rate. Drug concentration inside the blood will then remain constant and is said to be at the plateau state or the steady state concentration.

Infusion rate = Elimination rate
Rate of elimination of steady state = $Cl \times Cp_{ss}$
Rate of administration = $Cl \times Cp_{ss}$
Cl (total) = Cl (renal) + Cl (hepatic) + Cl (other)

Factors Affecting Steady state Plasma Concentration

Steady state plasma concentration is affected by the following factors

- Infusion rate which is directly proportional to the plateau state therefore increasing the rate in of the drug will increase the plasma concentration of drug at steady state.
- Plateau state is inversely proportional to the clearance rate of the drug.

The time to reach the plateau is determined by the elimination half-life of the drug, which results from clearance and volume of distribution. Thus, the V_d does not influence the steady state concentration but merely the time required to approach the plateau.

After 4 elimination half-lives the drug plasma concentration is 93,75% of the steady state plasma concentration. Likewise, when changing infusion

rates, the time required to reach the new steady state also depends on the half-life of the drug.

When stopping an IV infusion, the decline in plasma drug concentration follows an exponential curve, as after an iv-bolus injection of the drug.

Clinical Outcomes

The infusion at a constant rate is utilized to guarantee a consistent introduction of the drug in the body over a large period of time.Giancotti, L. Talarico, V. Mazza, G., A. Marrazzo, S, Gangemi, P. Miniero, R. Bertini, M. (2019). To attain a therapeutic range concentration of the drug in the body a constant infusion rate of drug should be maintained.

Precautions

Intravenous infusions oughtto be ceased or infusion li quid replenished when
the solution being administered is depleted.

Loading Dose

Loading dose is defined as the minimum effective dose which is given originally at a time to obtain the steady state plasma drug concentrations as early as possible.

Importance of Loading Dose

These are some of the important features of loading dose

- The main importance of loading dose is average plasma concentration at steady state as quickly as possible.
- In some cases, loading dose helps to urge therapeutic effect quickly.
- To attend fast plasma level.
- To attain fast action.
- To acquire desired concentration.

Calculations

We can calculate the loading dose by the followings

Loading dose= plasma concentration X volume of distribution / (Bioavailability X fraction of drug salt)
These are the variables that are used to calculate the loading dose:

Where C_p is desired peak concentration of drug
V_d is volume of distribution of drug in body
F is bioavailability
S is fraction of drug salt form which is active drug

For IV administration the drug quickly and directly goes to the blood stream hence the bioavailability of the drug will be equal to the 1. If the bioavailability of the drug is to be decreased below the one then it will be due to the Presystemic metabolism or limited absorption hence a greater loading dose will be required.

Continuous IV Infusion

We can give IV infusion of various fluids and drugs using a specific infusion rate and modifying the dosage regimen instead of giving a bolus at a time. This will avoid the interruption

Table 1. Complications with IV Infusion

Local Complications	Systemic Complications
• Infiltration	• Embolism
• Extravasation	• Pulmonary Embolism
• Thrombosis	• Air Embolism
• Thrombophlebitis	• Catheter Embolism
• Phlebitis	• Hematoma
	• Systemic infection
	• Speed shock
	• Circulatory overload
	• Allergic reaction

IV Infusion Devices

These are some of the IV diffusion devices discussed

- Cannula
- IV tubing set and solution bag.
- Tape
- IV pole or pump.

Dripping Rate

In an IV (intravenous) treatment, the drip rate is interpreted as the rate of application of a liquid drug required to deliver a certain dosage per minute.

An IV Infusion establish is used to allocate fluids and medications directly into the blood stream. Infusion or flow rates are modified to the desired drops per minute by a clamp on the tubing.

Calculation of IV Drip Rates: IV Infusion Rates Formula

x Drop Factor (gtts/mL) = IV infusion rat (gtts/min)

Note: Drops are always rounded to the nearest whole number.

Complications of IV Infusion

This is a table showing the most common complications of IV infusion

Multiple dose Regimen of Intravenous Administration

After a single quick IV injection, the maximum quantity of drug in the body is equal to the drug dose.

According to first-order kinetics, the drug will be eliminated for a one-compartment open model. Gai, X. Shen, N. He, B. Zhou, Q. Bo, S. Li, X. Zhai, S. Yin, A. Lu, W. (2015).

If τ is identical to the dosage interval, it is possible to determine the amount of drug that remains in the body after several hours.

Elimination constant and dosing interval determines the amount of the drug remaining in the body. as follows:

F=db/do

Amount of drug in the body will be less if the dosing interval will be less.

If the dose of 100 mg is given after each half-life then the dosing interval will be equal to half life.

After the first half-life of drug it will be 50mg.

After the second half-life of drug it will be 150mg.

After the third half-life of drug it will be 75mg.

After the fourth half-life of drug it will be 175mg.

This will continue until an equilibrium will be attained

Dmax =200mg and Dmin =100mg

Therefore the subsequent administration of the drug increases the body load and there is an absolute quantity of drug substance that is eliminated per unit time that's what is responsible for the first order kinetics means that drug going into the body is equal to the drug going out of the body.

If the value of f is known, a table can be constructed associating the fraction of the dose in the body before and after rapid IV injection.

Table 2: Fraction of the dose in the body before and after Intravenous administration

Table Fraction of the Dose in the Body before and after Intravenous Injections of a 1000-mg Dose		
	Amount of Drug in Body	
Number of Doses	Before Dose	After Dose
1	0	1000
2	250	1250
3	312	1312
4	328	1328
5	332	1332
6	333	1333
7	333	1333
∞	333	1333

Single Dose Regimen of IV Administration

When the interval of therapy is minor than the therapeutic activity of drug simple dose are provided in this manner. (Bastone, E. B., Li, S. C., Ioannides-Demos, L. L., Spicer, W. J., McLean, A. J. 1993) These are used in cases where therapeutic activity is required within no time or within seconds.

Conclusion

This review illustrates the importance of multiple dosage regimen that is used in treatment of chronic diseases as heart diseases and arthritis etc. Maintenance dosage regimen helps to improve clinical efficacy and therapeutic activity of the drugs decreasing the side effects and adverse drug reactions.

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